A demonstration project of Global Alliance against Chronic Respiratory Diseases: Prediction of interactions between air pollution and allergen exposure—the Mobile Airways Sentinel NetworK-Impact of air POLLution on Asthma and Rhinitis approach

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Abstract

This review analyzes the state and recent progress in the field of information support for pollen allergy sufferers. For decades, information available for the patients and allergologists consisted of pollen counts, which are vital but insufficient. New technology paves the way to substantial increase in amount and diversity of the data. This paper reviews old and newly suggested methods to predict pollen and air pollutant concentrations in the air and proposes an allergy risk concept, which combines the pollen and pollution information and transforms it into a qualitative risk index. This new index is available in an app (Mobile Airways Sentinel NetworK-air) that was developed in the frame of the European Union grant Impact of Air POLLution on sleep, Asthma and Rhinitis (a project of European Institute of Innovation and Technology-Health). On-going transformation of the pollen allergy information support is based on new technological solutions for pollen and air quality monitoring and predictions. The new information-technology and artificial-intelligence-based solutions help to convert this information into easy-to-use services for both medical practitioners and allergy sufferers.

Keywords: Pollen allergy; Pollen season; Google trends; Pollen dispersion modeling; System for Integrated modeLling of Atmospheric coMposition model; Pollen index; Air quality index

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Introduction

For patients allergic to pollen, knowledge of the season onset is of vital importance to start their treatment to control symptoms and avoid the disease exacerbations, such as asthma attacks. When traveling, patients are often concerned about potential symptoms outside their local environment: different pollen composition and concentrations, as well as different levels of atmospheric pollution can cause exacerbation of allergic symptoms. Few epidemiological studies have investigated the interaction between air pollution and pollen exposure on rhinitis symptoms[1-5] and more data are needed to quantify the impact of air pollution on allergic rhinitis (AR). The two major pollutants reported in connection to rhinitis so far are ozone (O_3) and fine particles ($PM_{2.5}$).

Mobile technology may help to better understand the links between air pollution, pollen, and allergic diseases. Mobile Airways Sentinel NetworK (MASK-air) is an information and communication technology system centered around the patient,[6-8] operational in 27 countries. It uses a treatment scroll list, which includes all medications customized for each country as well as visual analog scales (VASs) to assess the allergy, rhinitis, eye, and asthma symptom levels. Over 33,000 users and 200,000 VAS days have been recorded. MASK can be used to investigate the relationship between outdoor pollen and air pollutants and rhinitis and asthma symptoms.

Impact of air POLLution on Asthma and Rhinitis (POLLAR) is a project of the European Institute of Innovation and Technology-Health. The project embedded the environmental data into the MASK database and made it available for its users.[9] One of the objectives of POLLAR is to investigate the interaction between air pollution and pollen and its impact on the allergy symptoms.

Estimation of the Pollen Season

Pollen counts

Pollen counts are routinely used to assess the exposure of pollen-allergic patients.[10,11] However, the information obtained from most of the existing networks is not real-time and usually comes with a delay of a week or more. Also, the counts only partially correlate with symptoms since:

(1) Pollen counts do not necessarily represent the allergen exposure.[12-14] Allergens are also present in the air as sub-micronic particles that may induce symptoms.[15]
(2) Pollen samplers are usually placed at the top of a building.[16] The traps are well suited for estimating the regional mean airborne pollen concentration but may not provide an accurate personal exposure at the ground level.
(3) Patients live at variable distances from pollen samplers and are exposed to spatially-variable amounts of pollens, different from those at the traps locations. High costs of the predominantly manual pollen observations preclude establishment of dense networks. Thus, less than 900 pollen monitoring sites exist worldwide.[11] At the same time, there are over 10,000 and 40,000 operational air quality (AQ) sites in Europe (http://www.eea.eu) and the US (http://www.usepa.gov), respectively. Meteorological data flows vary from 10,000 to 100,000 datapoints per day depending on parameter, exceeding 1,000,000 datapoints per day for satellite observations.[17]
(4) The levels of allergens in pollen grains can vary strongly over a short period and between neighboring regions.[18,19] Considerable differences may exist in the allergen contents between the seasons or between early and late pollination of the same species. Olive pollen also shows substantial inter-cultivar variability.[20]
(5) Pollen concentrations that elicit symptoms are person-specific. They also vary between monosensitized and polysensitized subjects due to the overlapping pollen seasons[21] and the possible priming effect on the mucosa.[22] To increase the complexity, there is a non-linear effect of pollen and allergic symptoms.[23,24]
(6) Diversity of both exposure and sensitization levels makes it very difficult (or impossible) to find a "universal" concentration of pollen that is able to induce symptoms, that is, the clinical threshold. Some of these effects are accounted for in a new European Academy of Allergy and Clinical Immunology (EAACI) definition of pollen season including its onset and end, peak pollen days and peak pollen periods.[25-27]
(7) Simultaneous exposure to allergens and indoor or outdoor air pollution is common[28] and interactions between pollens and air pollution may exist,[1,29] leading to stronger symptoms and higher consumption of antihistamines at the same pollen level in case of poor AQ.[30]

Allergen content in the air

Assessment of the allergen content in the air is feasible using antibody-based methods[12,13,31] or the biomolecular identification of pollen genomes.[32] However, these sophisticated methods may not account for all pollen species in the air and availability of these methods for routine monitoring is very low due to high costs of the analysis. Bulky and expensive technology also precludes personalized or mobile allergen content measurements.

Real-time pollen observations

The real-time pollen observation is an emerging direction that is yet to become a mainstream. To date, overwhelming majority of pollen monitoring stations use the Hirst-type volumetric samplers.[10,33,34] With its simplicity, robustness, effectiveness, and low hardware costs, such pollen traps have become the reference all over the world.[11] However, these observations are quite uncertain: the technical design alone could bring 5% to 72% of measurement error,[35] whereas the manual counting contributes to additional 20% to 30% of uncertainty. The full cycle of pollen collection and counting typically takes 7 to 9 days.

In order to deliver real-time pollen data, next-generation pollen monitoring and dissemination systems based on robots have been established.[36] Two types of technologies are presently among the most-advanced. First, the Pollen-Sense (https://pollensense.com) and BAA500 (Hund Wetzlar, https://www.hund.de/en),[37] follow the classical approach automating the sampling and visual pollen recognition. Second, the air-flow cytometry devices, such as Waveband Integrated Bioaerosol Sensor/Spectral Intensity Bioaerosol Sensor,[38] Yamatronics KH-3000,[39] Plair Rapid-E,[40] and Swisens Poleno (http://www.swisens.ch), utilize the light-induced fluorescence of biological material, usually accompanied with scattering diagrams (eg, Rapid-E) or holograms (Poleno). Depending on the quality of the recognition algorithm, the information on the flying particle could be derived almost immediately with uncertainty approaching 20% to 30% or less depending on the taxon.[41,42] The pollen identification with all devices is based on manually collected and classified reference data sets and requires continuous manual correction and enrichment.

Arguably, the main problem of all devices with reasonable pollen recognition ability is their very high price. Other challenges include yet-to-mature quality control procedures, devices comparability even within the single type or brand,[43] and difficulties with identification of the "reference" pollen characteristics for every taxa, genus, and species.

The first operational multi-species pollen observational network was set in operations in Bavaria (Germany)[37] (https://epin.lgl.bayern.de/pollenflug-aktuell), equipped with the BAA500 devices. Since spring 2019, it provides 3-hourly data from eight monitoring locations. Also, in 2019, two Rapid-E devices were put into operations in Serbia and Croatia (http://www.realforall.com). That network is being extended in 2020 with the Rapid-E monitor in Lithuania and Rapid-E and Poleno devices in Finland. The geographical distribution of automatic pollen monitors as well as manual counters over the globe has been recently reviewed.[11]

Meteorological data and numerical models

Meteorological conditions are a vital driver of plant phenology, with flowering period being the key phenological phase relevant for the allergy sufferers. The most widely used and also the oldest concept is the heat-sum-based approach, which computes the amount of heat accumulated by the plants since the beginning of the growth season.[44-47] The developments suggested nearly-linear relation of "appropriately computed" heat sum and the stage of the flowering season.[48,49] Such models were shown to predict the onset of the flowering season within a few days of accuracy, about a week in advance. However, the pollen season depends on pollen long-range transport, which sometimes can make it dramatically different from the local flowering period.[50-54]

Accounting for the pollen release from inflorescences and subsequent transport in the atmosphere requires numerical models, which compute the whole lifecycle of pollen: maturation and presentation, release into the air, atmospheric transport and transformations, and deposition.[50,55,56] Such models currently can predict concentrations of up to six pollen types for up to 5 days for the whole Europe (http://atmosphere.copernicus.eu, http://silam.fmi.fi). The models COSMO-ART for Central Europe (http://www.meteoswiss.ch) and System for Integrated modeLling of Atmospheric coMposition (SILAM) for Northern Europe (http://silam.fmi.fi) perform high-resolution forecasts with grid-cell size of 1 and 2.5 km, respectively. Diversity of vegetation across the continents and severe lack of available observational data so far preclude development of hemispheric and global pollen dispersion models.

In Europe, an ensemble of continental-scale pollen models has been developed within the scope of Copernicus Atmospheric Monitoring Service (CAMS) (http://atmosphere.copernicus.eu), which has been shown to provide more robust predictions than individual models.[55] The pollen service is a part of the CAMS European AQ forecasting services.[57] CAMS AQ forecast is generated for up to 5 days over the globe and up to 4 days for Europe. With the open access to its products, CAMS supports many applications in a variety of domains including health, environmental monitoring, renewable energies, meteorology, and climatology.

The CAMS pollen developments are based on the pollen modules of SILAM[58] (http://silam.fmi.fi). SILAM performs operational pollen forecasts for six pollen species (alder, birch, grass, mugwort, olive, ragweed), trial forecasts for insects (aphids), and AQ forecasts for the globe, Europe and Asia, AQ hindcast for the previous day, as well as re-analysis of AQ from 1950 onwards. A variety of the data assimilation algorithms for pollen are under development,[50,55,59,60] including the use of the real-life symptom data obtained by the MASK-Air app.[61]

Internet and Google trends (GT)

Internet-based surveillance systems using search engine queries[62] and social media[63] are new techniques with the potential to extend the current monitoring systems.[64] The analysis of online searches, in particular using GT has shown potential in predicting changes in flu infections[65] and in other areas of medicine.[62] However, differences were found between GT and flu epidemics.[65-67] Recent studies have suggested that GT are also sensitive to allergic diseases.[68-71] GT data reflect the real-world epidemiology of AR and could potentially be used as a monitoring tool for AR.[72] However, different languages, terminology, cultural specifics, and information availability complicate the analysis and reduce its sensitivity.[73] In particular, for asthma, only massive outbreaks, such as thunderstorm-induced asthma, can be identified by GT.[74]

The 5-years-long GT analysis (2011–2016) in Europe showed a clear seasonality of pollen allergy-related queries in most countries. Different terms were found representative in different countries – namely "hay fever," "allergy," and "pollen" – showing the cultural differences.[73] The ragweed pollen allergy in GT was mainly associated with the term "ragweed," whereas the three terms identified in the first study ("pollen," "hay fever," and "allergy") did not correspond to the ragweed pollen season in eight out of 11 surveyed countries.[73] The term "ragweed" is mostly used in native languages whereas the direct translations by GTs are sometimes incorrect.[75] The "ragweed" queries were also visible during spring and summer, indicating that the tree and grass pollen allergy in spring may be perceived as "ragweed." As a result, the ragweed season found by GTs is far longer than the measured pollen season.[76]

A dedicated analysis for France over 2011 to 2016 showed similar findings in all French regions but only for spring and summer peaks. Wintertime pollen peaks were not reflected. Moreover, cypress pollen season is poorly represented in GT.[77]

Two GT studies were performed in Germany. Data from four pollen monitoring stations in the Berlin and Brandenburg area over 3 years (2014–2016) were used to investigate the correlation of season definitions, birch and grass pollen counts and total nasal symptom and medication scores as reported by patients in "Patients Hay fever Diary" (PHDs).[78] After the identification of pollen periods on the basis of the EACCI criteria, a statistical analysis was employed, followed by a detailed graphical investigation. The analysis revealed that the definitions of pollen season as well as peak pollen period start and end as proposed by the EAACI are overall but not exactly correlated to symptom loads for grass and birch pollen-induced AR reported by patients in PHDs. The same group analyzed the same data to examine the relationship between hay fever-related Google searches, symptom levels, medication use, and pollen counts. The analysis reveals that GT data are highly correlated with the symptom levels and reproduce the peak of the pollen season comparatively well.[79]

Taking all these studies together, it is likely that pollen seasons can be retrospectively analyzed using GT but some caveats need to be considered: (1) Only clear-cut seasons can be identified using GT. If there are overlapping seasons, pollen counts in some areas of the country need to be considered. There is also no information on the patients who posted the Google queries, which additionally blurs the picture in case of overlapping seasons. (2) It is likely that GT are easier to use in Northern Europe where there are only two major seasons (Betulaceae and grasses) than in Southern Europe where seasons of several species overlap. (3) In most countries, the ragweed pollen season cannot be studied using GT. (4) GT are extremely helpful retrospectively since aberrant queries can be assessed using the real-world monitoring data. However, for the prospective prediction GT are difficult to use. In particular, GT were initially used and then criticized for analysis and prediction of the flu epidemics[80,81] and virus infections.[82] Newer techniques can improve the estimation of the flu epidemics,[83] but aberrant peaks caused by various unrelated factors still pose a problem. GT may prove useful for forecasting the next pollen season as found for flu.[84,85]

Personalized Symptom Forecasting: Longitudinal Approach of Personal Allergy SYmptom FOrecasting (PASYFO) System

The first PASYFO system was developed as a use- case of the European CAMS service (http://www.pasyfo.lt and PASYFO App for iOS and Android) using the CAMS pollen and AQ forecasts. These forecasts were expanded with the SILAM six-pollens forecasts and combined with the PHDs symptom reports.[43,44] The symptom forecasting model (SFM) then utilized these retrospective data and generated the longitudinal personalized predictions of symptoms. The system prototype has been built for Baltic States but can cover any region with valid pollen and AQ forecasts and symptom reports.

The variables used by the PASYFO prototype from CAMS and SILAM forecasts include birch, grass, alder, mugwort, olive, and ragweed pollen, AQ parameters, such as sulfur dioxide, nitrogen dioxide, O_3, and $PM_{2.5}$ hourly concentrations, as well as the basic meteorological parameters, such as temperature, precipitation, cloudiness, wind speed, and humidity (https://atmosphere.copernicus.eu/pasyfo-forecasts-personal-allergy-symptoms). The SFM v.1 is a self-adjusting statistical model that learns from the retrospective time series generally following the technology[60] with appropriate modifications. The list of output parameters corresponds to that of the reported symptoms (for nose, eyes, and lungs in case of PHD).

Interactions Between Allergens and Pollutants

Associations between major air pollutants (O_3 and $PM_{2.5}$) and AR were studied during grass and birch pollen seasons as well as outside the pollen season in Northern Europe.[86] The daily load of allergic symptoms was recorded by the MASK-air® App using VAS in 2017 and 2018. Uncontrolled AR was identified from the reported symptom strength and applied medication. Pollutant levels were taken from the SILAM forecasts. Pollen seasons were assessed region-wise using GT and, if needed, pollen counts. Generalized estimating equation models were used to account for repeated measures per user, adjusting for gender, age, treatment, and country. The study showed that association between uncontrolled rhinitis and pollutants was stronger during the grass pollen season. An interquartile range increase in the O_3 level during the grass season was associated with an odds ratio of 1.25 (95% confidence interval [CI]: 1.11–1.41) in 2017 and of 1.14 (95% CI: 1.04–1.25) in 2018. A similar trend was found for $PM_{2.5}$, especially in 2017. These results suggest interactions between air pollution and grass pollen affecting the AR severity. There was no association with AQ during the birch pollen season.

The MASK-POLLAR Approach

The technology of MASK-POLLAR includes allergy symptom collection by the MASK-air® app,[6] related analytical software, European pollen and AQ forecasts (Europe and the globe) of SILAM. The SFM of PASYFO has been expanded with relevant statistical tools and prepared for the cross-sectional analysis of generalized allergy risk (as compared to the latitudinal approach of PASYFO). Attention was paid to the general data protection regulations compliance and personal-data protection via double encryption of the database and interfaces with the public-key cryptography (http://clem.dii.unisi.it/~vipp/files/MultimediaSecurity/MS_asymm_crypto.pdf).

Air quality index (AQI)

AQ is a public-health-relevant representation of atmospheric composition, often distributed as a single number of AQI, varying from 0 (good AQ) to 4 (very bad AQ).

The POLLAR implementation of the AQI for Europe followed the modified definition of the European Environment Agency (https://www.eea.europa.eu/themes/air/air-quality-index/index). In particular, the POLLAR AQI used hourly O_3 concentrations rather than the 8-h moving average. This modification followed the SILAM and CAMS standard temporal resolution, making the AQI more relevant to the allergy-related problems, where 8 h is a much too long averaging period. A similar definition of AQI is used by the United States Environmental Protection Agency (https://www.epa.gov/outdoor-air-quality-data/about-air-data-reports) with minor differences in its parameters.

Apart from the AQI value, the MASK-POLLAR system highlights the reason for the AQI elevation, that is, points out the component, which concentration is elevated. The daily-updated forecasts of AQI are available from the SILAM Web site http://silam.fmi.fi, AQ forecast section.

Pollen index

The second component of primary importance for the allergy sufferers is pollen index (POLind). The idea follows that of the AQI: a series of thresholds have been defined for each of the six pollen types predicted by SILAM (four of them are predicted by CAMS regional ensemble), which were projected to the scale from 0 to 4. The difficulty, however, is that there is no formal POLind definition since there is no pollen-related legislation at European level. Therefore, the current thresholds are based on expert opinions summarized in a book,[44] which was the main result of the European Cooperation on Science and Technology (COST) Action EUPOL (Assessment of production, release, distribution, and health impact of allergenic pollen in Europe).

Allergy risk index (ARI)

Assuming that pollen and the AQ are the dominant contributors to human pollen-related allergy, and the ARI can be constructed as a combination of the two. The MASK-POLLAR study showed the key AQ components exacerbating the pollen-induced allergy[85]: O_3 and $PM_{2.5}$. The sensitivity to poor AQ grows with the pollen season propagation due to the prolonged pollen exposure. Following this finding, the allergy risk is mainly driven by pollen presence in the air (pollen index) but can be modified by up to 20% by the AQ. A simple formula $ARI = POLInd + 0.2 * AQI$ sets the baseline representing the "mean" findings of POLLAR. The next version of the ARI will include dynamic day-to-day adjustments based on the MASK-Air reports. This adjustment will takes into account the pollen potency, interactions between the different AQ components and pollen species, non-linearity and mutual interactions between them, and so on. In the absence of the mechanistic models for these factors, they will be taken from the previous-days reports.

Summary

For patients allergic to pollen, forecast of the allergy risk is valuable information that can help in self-management of the disease and reduction of the symptom severity. It has been shown that this risk depends not only on concentrations of specific pollen in the air, but also on the allergen content of the pollen grains (pollen potency), concentrations of several atmospheric chemicals and aerosols, meteorological conditions, and so on. This information is currently available from the traditional pollen observations, new technologies of real-time monitoring, numerical models, and big-data analysis. Recent progress allowed for the first system of personalized allergy symptom forecasting and cross-sectional allergy risk assessment, which takes into account interactions between the pollen, AQ and allergy and asthma.

Conflicts of interest

None.

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